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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,061	03/10/2004	Lawrence J. Wangh	21578-010CON	5694

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,061	WANGH, LAWRENCE J.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 6, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87 and 89-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87 and 89-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 6, 2007 has been entered. Claims 87 and 89-98 are pending.

The obviousness-type double patent rejection over the claims in U.S. Patents 5,480,772, 5,651,992, 5,773,217 and 6,753,457 is withdrawn as proper terminal disclaimers have been filed on February 9, 2007.

This office action contains a new enablement rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 87-97 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/969,646 for reasons set forth in the office action mailed February 9, 2007.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant states a terminal disclaimer will be filed when allowable subject matter is indicated.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87 and 89-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for reprogramming a non-human animal somatic cell nucleus, comprising incubating said nucleus with a CSF extract of an MII egg followed by incubation of the somatic cell nucleus in a cytoplasmic extract of an induced egg, wherein said somatic cell nucleus is reprogrammed as indicated by nuclear swelling, nucleic acid replication and entry into mitosis, wherein said nucleus and said cell are of the same species;

a method for activating a somatic cell nucleus comprising incubating a somatic cell nucleus with the an CSF extract of a MII egg followed by incubation with an extract of an egg just prior to S-phase to yield an activated nucleus as indicated by nuclear swelling, nucleic acid replication and entrance into mitosis; and

a method of reprogramming a nucleus of a somatic cell to bring about nuclear activation comprising pretreating said nucleus to release said nucleus from surrounding cytoskeleton, incubating said pretreated nucleus with a CSF extract of an MII egg followed by incubation of said nucleus with an induced egg extract to activate said nucleus indicated by nuclear swelling, nucleic acid replication and entrance into mitosis,

does not reasonably provide enablement for incubation of a nucleus in an MII or induced egg, development of an embryo and indicators of activation other than nucleus swelling, nucleic acid replication and entry into mitosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 87 and 89-96 are not enabled for their full breadth as the specification fails to provide guidance for the claims as written. The specification teaches a method of reprogramming a somatic cells, as indicated by the somatic cell nucleus undergoing nuclear swelling, nucleic acid replication an entry into mitosis, by incubating a somatic cell nucleus in an "activating" cell extract produced from activated Xenopus oocytes prepared as disclose (specification, page 25). The method further incubates the activated nucleic in an extract prepared from MII-arrested Xenopus eggs, the extract containing a cytostatic factor for reprogramming the nucleic (specification, page 35, line 23).From the specification, the disclosed method critically requires both incubations for reprogramming, which is measured by the nucleus' undergoing nuclear swelling, nucleic acid replication and entry into mitosis. While the specification provides guidance on determining eggs from species other than Xenopus that could be used in both extract preparation (specification, page 31, line 33), the use of both extracts is required by the disclosure. Further, the specification discloses activation of several nuclei as shown by nuclear swelling, nucleic acid replication and entry into mitosis. However, there is no indication that cytokinesis occurred to produce a multicellular embryo. Without evidence of cytokinesis, embryo development will not occur. Further, the specification does not teach what contacting means. The specification is replete with incubation.

Thus, the method, as presently written, is unpredictable given the guidance in the specification.

Claims 97 and 98 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons set forth in the office mailed February 9, 2007. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 97 and 98 are to a method for cloning a non-human animal from a somatic cell nucleus. However, at the time of filing the art recognized that nuclear transfer or cloning to produce a term animal was unpredictable. Even if applicant's method results in a reprogrammed somatic cell nucleus, it is documented in the arena of nuclear transfer/cloning that pregnancy does not necessarily mean live births.

Applicant argues the unpredictability or inefficiency of maintaining pregnancy is inherent to all nuclear transfer methods. Applicant argues the method's efficiency is analogous to pronuclear injection techniques. Applicant argues the claimed invention has revolutionized nuclear transfer by increasing the efficiency of the process. Applicant argues that development of reconstructed embryos can be influenced by many factors, including quality of oocytes, methods of activation and culture methods. Similarly, applicant argues, maintenance of pregnancy is also dependent upon a range of factors. Applicant argues while it is possible to overcome the variables of development and pregnancy, it is overwhelmingly confirmed the use of an MII cytoplasm or unactivated egg cytoplasm that is required for reliable and successful reprogramming (specification, page 25, lines 21-26). Applicant argues the art did not teach the ability to produce a cloned animal from somatic cell nuclei, this crucial and enabling technology for cloning was provided by the present invention, incubation of a nucleus in the cytoplasm of an oocyte at MII followed by contacting the nucleus with the cytoplasm of an activated egg. These arguments are not persuasive.

Issue is taken with applicant's statement that nuclear transfer and pronuclear injection (used to produce transgenic animal by injection of a DNA sequence into a fertilized egg) have similar efficiencies. Schnieke provides evidence that nuclear transfer and pronuclear injection have vastly different efficiencies. In a comparison of pronuclear transgenesis and nuclear transfer, 982 pronuclear-injected oocytes yielded 1286 born lambs, 130% and 68 oocytes in nuclear transfer methods yielded 6 born lambs, 80% (Schnieke, page 2132, Table 3). Since applicant has not provided any comparison data to support their allegation that the methods are of comparable efficiencies, in view of Schnieke, there is no doubt that pronuclear injection is more efficient in yielding live births than nuclear transfer. While there is no doubt, as applicant states, that many factors affect term delivery in any nuclear transfer method, it also known the art that one of these factors is proper reprogramming, and that such reprogramming has to be sufficient to return the donor cell chromatin to the embryonic state. Hochedlinger (2006) states "reprogramming can be measured functionally by evaluating clone development at several different levels, including the rate of blastocyst formation, the fraction of cloned embryos surviving to birth or adulthood after implantation into the uterus, and the frequency with which pluripotent ES cells can be derived from cloned blastocysts explanted into culture" (page, 1061, col. 2, parag. 2, lines 8-13). With regard to reprogramming using Xenopus extracts such disclosed in the specification, Hochedlinger states "no stable reprogramming was seen in reversibly permeabilized somatic cells that were subsequently passaged in culture, suggesting that an intact oocyte might be required for functional de-differentiation to a pluripotent state" (page 1064, col. 1, parag. 4, lines 15-18). Thus, the art is clear that reprogramming is essential for term birth of a cloned animal, and incubation in Xenopus extracts is unpredictable in its ability to sufficiently reprogram a differentiated cell nucleus to support term development. While applicant has developed a method that shows some features of reprogramming,

nuclear swelling, nuclear DNA replication and entry into mitosis of the donor cell, there is no evidence on this record that such reprogramming is sufficient to lead the donor cell to direct development of the donor cell into a live-born animal.

Further it is noted that the specification teaches the treatment of permeabilized donor nuclei subsequently with two Xenopus egg extracts, first an MII activating egg extract and second non-activated CSF egg extract. (see specification, page 23, lines 17 to 34; page 25, lines 8-13 and page 34, lines 15-26). There is no enablement for exposure directly to egg cytoplasm of any variety.

It is also noted that cross-species nuclear transfer is regarded as unpredictable. As stated in the office mailed March 23, 2006, Meirelles demonstrates that methods of nuclear transfer where the nuclear material of *Bos indicus* is inserted into the oocyte of *Bos taurus* produces calves comprising the nuclear material of *Bos indicus* and the mitochondria of *Bos taurus*. Meirelles *et al.* teach that previous attempts to use the *Bos* oocyte as hosts for nuclear transfer from unrelated species allowed development to the blastocyst stage, and conclude that incompatibility among the nuclear and mitochondrial genetic systems is responsible for the early arrest. Meirelles also points to similar failures using *Mus caroli* and *Mus musculus* citing Dominko. Meirelles conclude stat in light of their results and the failures of the prior art, that nuclear transfer across subspecies barriers is possible. (see Meirelles, pp. 351-355). There is no evidence on this record to overcome the teachings of Meirelles.

Applicant argues Bour'hic, Fariburn and Hill state reprogramming is the root cause of nuclear transfer inefficiency and unpredictability. Application argues that Bour'hic, Fairburn and Hill also teach new information will clarify the causes and extension of the observed variability or inefficiency. Applicant argues Hou shows DNA methylation reprogramming in bovine embryos is also affected by in vitro maturation, fertilization and culture. Applicant argues the level of efficiency or unpredictability is within range of that accepted by the

artisan. Applicant argues Bour'hic did not anlalyze any genes known to be involved in embryonic development and euchromatic methylation patterns before implantation were similar in normal and cloned embryos. Fairburn, applicant argues, states reprogramming is not responsible for the low birth rates and developmental abnormalities seen in nuclear transfer. Applicant argues Fairburn states data derived from any methylation studies lacks direct evidence of aberrant patterns associated with abnormal gene transcription in cloned embryos. Applicant argues Hill teaches the gestational and neonatal abnormalities seen in nuclear transfer are consistent with irregular expression and likely incomplete reprogramming, but provides no direct evidence to support this conclusion. Applicant argues Corcoran provides further evidence that culture conditions alone can cause changes in the expression profiles of genes known to be involved in development. These arguments are not persuasive.

As applicant admits, reprogramming is a critical issue in nuclear transfer. Hochedlinger, discussed above, supports the criticality of reprogramming. The present record provides only evidence of nuclear swelling, nucleic acid replication and entry into mitosis. These events are not correlated with a term birth, especially with Hochedlinger commenting that contact with an egg cytoplasm, not just an egg extract, maybe required. Corcoran does not provide for enablement, as there is no evidence of a term birth following exposure to egg extracts.

Applicant argues the claims require a cytoplasm of an MII oocyte and an activating egg cytoplasm. Applicant argues the teachings of extracts are exemplary uses of MII oocyte cytoplasm and activating egg cytoplasm. Applicant argues they have identified these as reprogramming tools, and others have confirmed the success of using these tools in either forms citing Sullivan et al. These arguments are not persuasive.

Sullivan uses an extract from a somatic cell line, MDBK cells, whereas the specification only discloses using an MII egg extract to activate donor nuclei. Sullivan does not, therefore, support the enablement of the claimed invention as the methods used therein are materially different.

Applicant argues Polejaeva teaches the production of cloned pigs by serial nuclear transfer by first placing a somatic cell nucleus in an MII oocyte, followed by transfer into a zygote. This argument is not persuasive.

Nothing the specification contemplates or teaches the method of Polejaeva. Applicant's methods are to the use of MII egg extracts for the activation step. The specification does not disclose activation by transfer of a nucleus into an MII oocyte (specification, page 59, lines 5-9 and 15-19). Polejaeva uses intact oocytes or intact zygotes as the incubating cytoplasm. Applicant's specification does not disclose the method of Polejaeva. Again it is emphasized, the present specification only contemplates the use of extracts to reprogram/activate somatic cell nuclei.

Applicant argues the specification shows cross-species activation of somatic cell nuclei in that Xenopus egg extracts activate human erythrocyte and sperm nuclei. This argument is not persuasive.

The subject matter of claims 87, 97 and 98 encompass the production of a cloned mammal. The art of Hochedlinger and Meirelles provide evidence that cross species nuclear transfer is unpredictable for the production of a cloned animal. While nuclear activation may occur and some degree of embryo development, the production of a cloned animal is not predictable.

Therefore the skilled artisan would need to engage in a due amount of experiment without a predictable degree of success to implement the invention as presently claimed.

Claims 87 and 89-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter,

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The invention as claimed encompasses incubation of a somatic cell nucleus in an intact MII egg followed by incubation in an intact induced egg. However, a review of the specification does not reveal this invention was disclosed. If an invention is not disclosed in the specification, then there is no evidence that applicant contemplated the invention. An invention that is not contemplated cannot be later claimed.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggest methods of nuclear transfer, where the donor nucleus was incubated first in a cytostatic egg extract and second in an activating egg extract.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

July 31, 2007